

REMARKS

Claims 1-14 and 17-34 are currently pending. A clean version of the pending claims is submitted herewith as Appendix A.

Applicants respectfully request reconsideration of the pending claims 1-14 and 17-34.

I. Objection to Under 35 U.S.C. § 132

The Amendment filed 05 November 2001 has been objected to under 35 U.S.C. § 132 as allegedly introducing new matter into the disclosure. The Examiner opines that the amendments to pages 56, 59 and 60 of the specification for failing “to have adequate written description support in the application as-filed” (Office Action, page 2).

Applicants respectfully traverse this objection.

In the Preliminary Amendment, filed on 05 November 2001, Applicants amended the specification to insert text relating to the ability of the 5G1.1 antibody to bind to both the alpha and beta chains of human C5 protein, as determined by immunoblot assay. After entry of this amendment, the text of Example 8 of the instant application exactly corresponds to the text of Example 7 in Wang et al. (U.S. Patent No. 6,074,642 (hereafter the ‘642 patent), columns 18-19, (submitted previously). The Wang *et al.* application (U.S. Serial No. 08/236,208), which evolved into the ‘642 patent, was incorporated by reference into the specification of the instant application in its entirety (see page 6, lines 6-7 and page 60, lines 11-16).

"The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the application as filed. Replacement of the identified material incorporated by reference with the actual text is not new matter." (M.P.E.P. § 2163.07(b). See also *Mendenhall v. Astec Industries Inc.*, 13 USPQ2d 1913, 1922 (E.D. Tenn. 1988), aff'd, 887 F.2d 1094, 13 USPQ2d 1956 (Fed. Cir. 1989) (unpublished) ("A patent application may comply with 35 U.S.C. § 112 by incorporating by reference the disclosure of another pending United States patent application."); *Ernsthause v. Nakayama*, 1 USPQ2d 1539, 1547 (Bd. Pat. App. & Int'l 1985), aff'd, 809 F.2d 787 (Fed. Cir. 1986) (unpublished) ("An application for a patent when filed may incorporate essential material by reference to a United States patent"). Therefore, Applicants have not added new matter to the specification by way of the 05 November 2001 Preliminary Amendment, as the added text was identical to text in a patent application, which was incorporated by reference in its entirety in the as-filed application.

Thus, contrary to the Examiner's assertions, no new matter was added by way of the 05 November 2001 Preliminary Amendment.

Accordingly, Applicants respectfully request that this objection be reconsidered and withdrawn.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 19-34 have been rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification does not contain written description of the claimed invention and

does not reasonably convey to one of skill in the art that Applicants had possession of the claimed invention.

Applicants respectfully traverse this ground of rejection.

The Examiner opines that “generic disclosure” of C5 blockers on pages 56 and 59-60 of the specification does not provide adequate written description support for the antibodies which “bind to the alpha chain of C5.” However, Applicants respectfully direct the Examiner’s attention to the Amendments to the specification submitted on 05 November 2001 (05 November 2001 Preliminary Amendment, Appendices A-D), which have been entered by the Examiner (Office Action, page 2). Thus, after entry of these amendments¹, the specification on, e.g., pages 59-60, now reads

The supernatant from a hybridoma designated as 5G1.1 tested positive by ELISA and substantially reduced the cell-lysing ability of complement present in normal human blood in the chicken erythrocyte assay. Further analyses revealed that the 5G1.1 antibody has two surprising properties: 1) it reduces the cell-lysing ability of complement present in normal blood so efficiently that, even when present at roughly one-half the molar concentration of human C5 in the hemolytic assay, it can almost completely neutralize serum hemolytic activity; and 2) it binds to both the alpha and beta chains of the human C5 protein.

The surprising and unanticipated ability of the monoclonal antibody produced by hybridoma 5G1.1 (the 5G1.1 mAb) to bind to both the alpha and beta chains of the human C5 protein was revealed when immunoblot analysis was undertaken to further characterize the 5G1.1 mAb. Human C5 (Quidel Corporation, San Diego, Calif., Catalog No. A403) was subjected to polyacrylamide gel electrophoresis under reducing conditions, transferred to a nitrocellulose membrane, and probed with the 5G1.1 mAb as a purified IgG preparation. Two bands were immunoreactive with the 5G1.1 mAb at apparent molecular weights

¹ Applicants note that the 05 November 2001 Amendments to the specification are supported in the application as-filed because the text exactly corresponds to text in the Wang *et al.* application, which was incorporated by reference in its entirety in the as-filed application. See pages 2-3 *supra* for further discussion. Accordingly, it is believed that no issue of new matter arises.

corresponding to those of the alpha and beta chains of the human C5 protein.

Thus, it will be appreciated that there is adequate written support in the specification for antibodies which bind the alpha chain of C5.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Claims 18 and 34 also stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

Applicants have described on page 60 of the specification that deposit of hybridoma 5G1.1 was made on 27 April 1994 with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209. The deposit has been assigned the ATCC Accession Number HB-11625. The deposit has been made under the terms of the Budapest Treaty and all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent.

Accordingly, Applicants respectfully request that this ground of rejection be reconsidered and withdrawn.

III. Rejection Under 35 U.S.C. 102(e)

Claims 1-17 have been rejected under 35 U.S.C. § 102(e) over Sims *et al.* (U.S. Patent No. 5,635,178).

Applicants respectfully traverse this ground of rejection.

Sims *et al.* does not teach a method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5. Instead, Sims *et al.* teaches a monospecific rabbit antibody against the purified human erythrocyte 18 kDa protein (α -P18) (Col. 7, lines 36-38). The α -P18 antibody binds to the 18 kDa protein on the erythrocyte membrane and prevents the C5b-9 complex from forming on the platelet surface (Col. 9, line 40). Further, Sims *et al.* states that

[a]s used herein in the compositions and methods for the prolongation of platelet and organ survival and enhancement of therapeutic efficacy or suppression of complement mediated disorders, "C5b-9 inactivator" refers to the 37 kDa protein from platelets, the corresponding 37 kDa protein on endothelial cells, the 18 kDa protein on erythrocyte membranes, peptide fragments thereof having C5b-9 inhibitory activity, and preferably containing a membrane binding domain, whether isolated from naturally produced materials or recombinantly engineered sequences, monoclonal antibodies to C7 that block membrane binding of the C5b-9, monoclonal antibodies to C9 that block C9 polymerization and insertion into the membrane, monoclonal antibodies that blocks C9 binding to C5b-9, and anti-idiotypic antibodies which inhibit the function of the cell surface molecules in inhibiting C5b-9 activity, especially the Fab fragments of monoclonal antibodies having this activity. All molecular weights are determined by SDS-PAGE under non-reducing conditions. The 37 kDa and 18 kDa proteins are species specific, i.e., only inhibitor proteins of human origin will inhibit human C5b-9. Col. 5, lines 30-51.

Thus, Sims *et al.* does not teach antibodies specific for C5 as recited in claims 1-17, or specific for the alpha chain of C5 as recited in claims 18-34.

Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

IV. Rejection Under 35 U.S.C. 103(a)

Claims 1-14 and 17-34 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sindelar *et al.* (U.S. Patent No. 5,173,499) and/or Sims *et al.* in view of Auda *et al.* (Rheumatol. Int. 10:185-18 (1990)), Wurzner *et al.* (Complement Inflamm. 8:328-40 (1991)) and Montz *et al.* (Cell. Immunol. 127:337-51 (1990)) in further view of Rollins *et al.* (U.S. Patent No. 5,853,722).

This ground of rejection is respectfully traversed.

The Examiner states that Sindelar *et al.* teaches methods for treating established joint inflammation comprising the administration of an effective amount of a C5 blocker. Sims *et al.* is cited to teach antibodies which specifically bind to a component forming the C5b-9 complex. Auda *et al.* is cited to teach the measurement of complement activation products in patients suffering chronic rheumatic diseases to predict patient clinical status. Auda *et al.* is also cited to teach monitoring C5b-9 levels in patients to provide a more sensitive indicator of patient status. Wurzner *et al.* is cited to teach the inhibition of terminal C components by monoclonal antibodies specific for C5. Montz *et al.* and Wurzner *et al.* are further cited to teach C5 inhibitors, which do not affect the early C components. The Examiner asserts that one of ordinary skill in the art would have been motivated to modify the teachings of Sindelar *et al.* with the teachings of Auda *et al.*, Montz *et al.* and Wurzner *et al.* to use C5 inhibitory antibodies to inhibit inflammatory joint disease. The Examiner contends that the motivation to combine the references is in the use of analogous compounds to those taught in Sindelar *et al.* for the inhibition of C5 activity with a reasonable expectation of success, although the Examiner does

not appear to contend that the asserted motivation may be found within the cited references themselves. (*See* 03/31/96 Office Action).

"To establish a *prima facie* case of obviousness based on a combination of the content of various references, there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998); *see also In re Dembicza*k, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); *In re Mayne*, 104 F.3d 1339, 1342, 41 USPQ2d 1451, 1454 (Fed. Cir. 1997) ("When relying on numerous references or a modification of prior art, it is incumbent upon the examiner to identify some suggestion to combine references or make the modification."); *In re Paulsen*, 30 F.3d 1475, 1482, 31 USPQ2d 1671, 1676 (Fed. Cir. 1994) ("In reviewing the Board's obviousness conclusions, we have been guided by the well-settled principles that the claimed invention must be considered as a whole, *multiple cited prior art references must suggest the desirability of being combined*, and the references must be viewed without the benefit of hindsight afforded by the disclosure") (emphasis added).

Applicants respectfully direct the Examiner's attention to the Declaration of Dr. Yi Wang pursuant to 37 C.F.R. § 1.132, which was submitted 12 September 1996. Dr. Wang declares that it was not known that the method claimed in the instant application would be successful in treating established joint inflammation. Indeed, published references taught away from the present invention, *i.e.*, they taught that animals carrying a genetic defect, which caused them to

have no C5, still developed established joint inflammation (Wang Declaration, paragraph 4, and references cited therein). As Dr. Wang pointed out in his Declaration, based on the teaching of these prior art references, one skilled in the art would have expected that inhibiting C5 in mice would fail to treat established joint inflammation; thus, it was wholly unexpected that administering antibodies specific against C5 to mice would treat established joint inflammation, as was surprisingly discovered by Dr. Wang and his co-inventors (Wang Declaration, paragraph 4).

The Sindelar *et al.* patent is directed to chemically synthesized non-protein organic compounds, which are substituted dihydrobenzofurans, spirobenzofuran-2(3H)-cycloalkanes, and their open chain intermediates, for the inhibition and/or suppression of immune activity (Sindelar *et al.*, abstract). As the Examiner implicitly acknowledged in withdrawing the prior rejection under 35 U.S.C. § 102(b) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over the Sindelar *et al.* reference, Sindelar *et al.* does not teach or suggest methods for the treatment of established joint inflammation using a composition comprising a purified antibody specific against C5. Further, with respect to claims 19-34, Sindelar *et al.* also does not teach or suggest methods for the treatment of established joint inflammation using a composition comprising a purified antibody, which binds the alpha chain of C5.

Sims *et al.* is cited to teach antibodies which specifically bind to a component forming the C5b-9 complex. However, as described in more detail elsewhere herein, Sims *et al.* does not teach antibodies specific for C5 as recited in claims 1-17, or specific for the alpha chain of C5 as recited in claims 18-34.

In an attempt to cure the deficiencies of Sindelar *et al.* and Sims *et al.*, the Examiner cites Wurzner *et al.*, which teaches the production of two monoclonal antibodies, allegedly specific for C5.

Wurzner *et al.* fails to supply does nothing to correct the deficiencies of Sindelar *et al.* or Sims *et al.* As described above, neither Sindelar *et al.* or Sims *et al.* does not teach or suggest methods for the treatment of established joint inflammation using a composition comprising a purified antibody specific against C5. Similarly, Wurzner *et al.* does not teach or suggest, and is not enabling for, the use of antibodies specific against C5 for the treatment of established joint inflammation. Wurzner *et al.* teaches the production of two monoclonal antibodies. Based on *in vitro* testing, these antibodies are stated to be specific for C5. Wurzner *et al.* does not describe any *in vivo* studies to show that the antibodies would be effective *in vivo*, much less effective for the treatment of established joint inflammation, as was shown of the antibodies used in the instant application (see *e.g.*, Examples 1 and 2).

Moreover, the prior art references fail to provide the requisite motivation to substitute the teachings of Sindelar *et al.* or Sims *et al.* with Wurzner's monoclonal antibodies directed against C5. At best, the Wurzner reference only speculates that such C5 antibodies may be useful to arrest the complement cascade, which may be beneficial for some diseases. In fact, while the authors speculate that the C5 antibodies may be useful to arrest the complementary cascade, they fail to teach or suggest the stage at which to arrest the complement cascade to achieve clinical usefulness:

Arresting the complement cascade at an earlier stage may not be the most clinically useful point to prevent TCC formation because both activation pathways as well as cleavage of C5 by injured tissue-related enzymes...or C5

activation by oxygen radicals...would have to be blocked. Arresting the complement cascade at a later stage, as shown with anti-C8 mabs..., will neither inhibit membrane insertion of the terminal complement complex nor C5a liberation. (Wurzner at 337; citations omitted).

Wurzner's uncertainty and speculation do not provide the requisite motivation to substitute the Wurzner monoclonal antibodies for the Sindelar C5 blockers. Mere conjecture is not the appropriate standard for obviousness. *Datascope Corp. v. SMEC, Inc.*, 224 U.S.P.Q. 694, 698 (D.N.J. 1984), *aff'd in part & rev'd in part* 776 F.2d 320, 227 U.S.P.Q. 838 (Fed. Cir. 1985) ("Anticipation cannot be predicated on teachings in a reference that are vague or based on conjecture").

Similarly, Wurzner *et al.*, either alone in combination with Sindelar *et al* and/or Sims *et al.*, does not anticipate or render obvious claims 19-34, which recite a method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody, which binds the alpha chain of C5. Specifically, Wurzner *et al.* discusses the production of two monoclonal antibodies, N19-8 and N20-9, which are specific against the beta chain of C5 (see Wurzner *et al.*, page 337, left column, lines 4-6). The specific use of these C5 beta chain-specific antibodies to treat joint inflammation is not taught or suggested. Applicants submit that the effective use of a composition comprising a purified antibody, which binds the alpha chain of C5, in a method for the treatment of established joint inflammation, was not known in, much less suggested by, the prior art including Wurzner *et al.*, and thus that Wurzner *et al.* does not supply the deficiencies of Sindelar *et al.* and/or Sims *et al.*. Thus, claims 19-34 also distinguish over Wurzner *et al.*, alone or in combination with any other reference of record.

In a further attempt to cure the deficiencies of Sindelar *et al.* and Sims *et al.*, the Examiner cites Montz *et al.* However, the Montz *et al.* reference does nothing to correct the deficiencies of Sindelar *et al.*, Sims *et al.*, and/or Wurzner *et al.* Montz *et al.* discusses experiments to determine the potential role of endogenously synthesized C5 and subsequently generated C5a in *in vitro* autologous T cell stimulation. Montz *et al.* is directed to analyzing the inhibitory effect of anti-C5a against autologous T cell proliferative responses *in vitro*. Montz *et al.* does not teach or suggest an *in vivo* method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5. Similarly, Montz *et al.* does not teach or suggest an *in vivo* method for the treatment of established joint inflammation in a patient in need thereof comprising administering to the patient an effective anti-inflammatory amount of a composition comprising a purified antibody, which binds the alpha chain of C5, as required by claims 19-34. Therefore, neither Wurzner *et al.* nor Montz teaches or suggests the use of anti-C5 antibodies to treat established joint inflammation in a patient, and thus neither supplies the deficiencies of Sindelar *et al.* or Sims *et al.*, alone or in combination.

The Examiner cites Auda *et al.* which, respectfully, does nothing to remedy the deficiencies of Sindelar *et al.*, Sims *et al.*, Wurzner *et al.*, and Montz *et al.* Auda *et al.* merely describes measuring complement activation products in patients. While it is an interesting fact that C5b-9 complex levels were increased in patients with chronic rheumatic diseases, as discussed above, mouse studies in which C5 was completely absent due to a genetic defect continued to develop established joint inflammation (Wang Declaration). In response, the Examiner asserts that the Declaration is found unpersuasive because Auda *et al.* “clearly

indicates the involvement of complement in rheumatoid arthritis and the recruitment of PML.”

However, in addition to showing that C5b-9 complex levels were elevated in patients with chronic rheumatic diseases, Auda *et al.* also showed that early complement component complexes (in addition to the late complement component C5b-9 complex) were also increased in patients with chronic rheumatic diseases. In fact, C1s:C1-inh, C3bP and C5b-9 complexes were each elevated in all patients (see entire document).

Moreover, Auda *et al.* makes the merely precatory suggestion that “monitoring the levels of complement activation products may provide additional information and allow predictions of clinical status.” Similarly, Auda *et al.* does not suggest use of the alpha chain of C5, as required by claims 19-34. The authors do note that the predictive value of a test utilizing C5b9 has been shown in determining the onset of adult respiratory distress syndrome (which is not a disease of established joint inflammation), which allegedly suggests C5b9 may provide a more sensitive indicator than measurements of CH50, C4a, C3a or C5a” (page 188, right column, second full paragraph). However, once again, there is no indication of which of the many complement components found in elevated levels in the blood or patients with chronic rheumatic diseases is most important. There is similarly no indication of the importance of the alpha chain of C5. There is also not any suggestion in Auda *et al.* that antibodies specific against C5 would be useful in treating patients with established chronic joint inflammation, as required by claims 19-34. Thus, Auda *et al.* does not teach or suggest the claimed method of treating established joint inflammation by administering to a patient either a composition comprising a purified antibody specific against C5, or a composition comprising a purified antibody which binds to the alpha chain of C5. Further, Auda *et al.* does not provide any motivation to combine the references cited by the Examiner.

The Examiner asserts that Rollins *et al.* is added to allegedly provide further teachings and evidence that C5-specific antibodies had the property of inhibiting complement inflammatory conditions in humans at the time the invention was made.

The Sindelar *et al.*, Sims *et al.*, Auda *et al.*, Wurzner *et al.*, and Montz *et al.* references are discussed above. Rollins does not remedy the deficiencies of the combination of Sindelar *et al.* and/or Sims *et al.*, in view of Auda *et al.*, Wurzner *et al.*, and Montz *et al.*. Rollins teaches the use of anti-C5 antibodies to block the generation of activated complement components C5a and C5b following extracorporeal circulation during cardiopulmonary bypass. Indeed, Rollins specifically teaches that “[m]ore generally, the invention relates to the use of anti-C5 antibodies in any procedure which involves circulating the patient’s blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient” wherein the “anti-C5 antibody is used to reduce at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion resulting from the circulation of the patient’s blood through such a conduit” (Rollins, columns 10-11). In contrast, the methods of treating established joint inflammation encompassed by the claimed invention are directed to administering, to a patient, an effective anti-inflammatory amount of a composition comprising a purified antibody specific against C5.

Thus, Rollins does not supply the deficiencies of Sindelar *et al.*, Sims *et al.*, Auda *et al.*, Wurzner *et al.*, and Montz *et al.*. Further, the motivation to combine the references is lacking, because none of the prior art references suggests the desirability of modification of the references.

It is not sufficient that the prior art *could be* modified to produce the claimed invention. Rather, the modification is non-obvious unless the prior art suggests the desirability thereof. *In re Laskowski*, 10 USPQ2d 1397 (Fed. Cir. 1989). Further, the invention as a whole must be considered when determining obviousness, and it is improper to consider only the obviousness of any substitution or modification. *Hybritech v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed. Cir. 1986). Indeed, modification of the teachings of a prior art reference is not established by the teachings of a second prior art reference "*unless the prior art suggests the desirability of the modification.*" *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (emphasis added).

Applicants respectfully submit that the required motivation to combine the Sindelar *et al.*, and/or Sims *et al.*, Auda *et al.*, Wurzner *et al.*, Montz *et al.*, and Rollins *et al.* references is completely lacking. Not one of these references, either alone or in combination with the other references, discloses or suggests to the ordinarily skilled person the desirability of the claimed invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

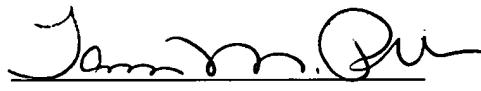
V. Conclusion

In view of the foregoing remarks, Applicants respectfully submit that this application is now in condition for immediate allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a three (3) month Extension of Time under 37 C.F.R. § 1.136(a) is filed concurrently herewith, which extends the response period from 24 April 2002 to 24 July 2002. The Petition further authorizes the PTO to charge the three month extension fee of \$920 to our Deposit Account No. 08-0219.

Applicants believe no other fees are due in connection with this Amendment. However, if there are any other fees due, please charge them to Deposit Account 08-0219. Also, please credit any overpayment to the same Deposit Account.

Respectfully submitted,



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